Contains Nonbinding Recommendations

Draft Guidance on Leuprolide Acetate / Norethindrone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Leuprolide acetate; Norethindrone acetate

Dosage Form; Route: Injectable depot / tablet; intramuscular / oral

Recommended Studies: Two in vivo studies

Additional Comments: The proposed test parenteral drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference product for all strengths. Please provide characterization data on polylactic acid (PLA) or poly(lactide-co-glycolide) (PLGA) for both the test and reference products including, but not limited to, polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and polymer architecture (e.g., linear or star-branched). Additional PLA or PLGA polymer, and drug product characterization data may be requested during the review of the ANDA.

1.	Type of study:	Bioequivalence study with pharmacokinetic endpoints
	Design:	Single-dose, randomized, parallel, in vivo
	Strength:	11.25 mg/vial (Leuprolide acetate injectable depot 3-month)
	Subjects:	Endometriosis patients who are receiving treatment with leuprolide acetate and norethindrone acetate for their condition
	Additional Comment:	Subjects should not be pregnant or lactating. Subjects should co-administer 5 mg norethindrone acetate tablet daily during the study.

2.	Type of study:	Bioequivalence study with pharmacokinetic endpoints
	Design:	Single-dose, randomized, parallel, in vivo
	Strength:	3.75 mg/vial (Leuprolide acetate injectable depot 1-month)
	Subjects:	Endometriosis patients who are receiving treatment with leuprolide acetate and norethindrone acetate for their condition
	Additional Comment:	Please see comments above.

3.	Type of study:	Bioequivalence study with pharmacokinetic endpoints
	Design:	Steady state, crossover, in vivo

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

Strength: 5 mg (Norethindrone acetate tablet)
Subjects: Endometriosis patients who are enrolled in study 1 or study 2
Additional Comment: None

Analytes to measure (in appropriate biological fluid): Leuprolide in serum (study 1 and study 2); Norethindrone in plasma

Bioequivalence based on (90% CI): Leuprolide; Norethindrone

For leuprolide, the 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{7\text{-}t}$, AUC_t, $AUC_{0\text{-}\infty}$, and C_{max}, where $AUC_{7\text{-}t}$ is the area under the plasma-concentration vs. time curve from 7 days to the last measurable sampling time point, AUC_t is the area under the curve from 0 to the last sampling measurable time point, $AUC_{0\text{-}\infty}$ is the area under the curve from 0 to infinity, and C_{max} is the maximum plasma concentration.

For norethindrone, the 90% confidence intervals of the following PK parameters must meet the acceptable limits of [80.00-125.00]: Log-transformed $AUC_{0\text{-}tau}$, and C_{max}, where $AUC_{0\text{-}tau}$ is the area under the curve to the end of the dosing period at steady state, and C_{max} is the maximum plasma concentration during the dosing interval.

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods web site, available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).